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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/584,447	07/09/2007	Tomoaki Takakura	0032-0291PUS1	4157

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EXAMINER
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EPPS -SMITH, JANET L

ART UNIT	PAPER NUMBER
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1633

NOTIFICATION DATE	DELIVERY MODE
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01/19/2012

ELECTRONIC

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

<b>Office Action Summary</b>	<b>Application No.</b> 10/584,447	<b>Applicant(s)</b> TAKAKURA ET AL.	
	<b>Examiner</b> Janet Epps-Smith	<b>Art Unit</b> 1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 04 November 2011.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-10, 12 and 17 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-10, 12 and 17 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 02 June 2010 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)          | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____  | 6) <input type="checkbox"/> Other: _____                          |

### **DETAILED ACTION**

1. Claims 1-10, 12 and 17 are presently pending for examination.
2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

#### ***Claim Rejections - 35 USC § 102***

3. The rejection of claims 1-6 under 35 U.S.C. 102(b) as being anticipated by El Tayar et al. (WO99/55377) is withdrawn.

#### ***Claim Rejections - 35 USC § 103***

4. The rejection of claims 1-10, and 12 under 35 U.S.C. 103(a) as being unpatentable over El Tayar et al. as applied above in view of Tan et al. (WO/9640284A1) is withdrawn.
5. Claims 1-10, 12, and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Roberts et al. (US 2003/0105224A1) in view of Nihon Shineikagakkai Ed., Shinsei-kagaku Jikken Kouza 1: "Tanpakushitsu N: Kouzou kinou soukan" (20 March 1991), pp. 95-111 (Document #2), and Tan et al. (WO/9640284A1).
6. Roberts et al. describes a method for conjugating polymers specifically to the alpha-amine of polypeptides. The method provides monofunctional, bifunctional, and multifunctional PEGs and related polymers having a thioester moiety capable of specifically conjugating to the alpha-amine of a polypeptide having a cysteine or histidine at the N-terminus.
- 7.

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8. Roberts et al. does not teach the synthesis of polymer conjugates of methioninase or the reaction of protein-polymer conjugates with a thiol compound.

9. Document #2 describes that SH groups in a protein are easily modified by various chemical substances, and that the chemical modifications of SH groups in papain and various other proteins can be removed by DTT and other thiol compounds, thereby restoring activity.

10. Tan et al. at page 3, provides a brief description of the invention:

It has now been discovered that methioninase, either in PEGylated form or as produced and purified as a highly pure, endotoxin free recombinant form, can deplete levels of methionine in mammals without harm, can be effectively used to selectively inhibit tumor growth and further can be used to selectively arrest and thereby synchronize tumor cells for antimitotic chemotherapy.

Tan et al. further discloses the following: A chemically modified methioninase comprising methioninase conjugated to a polymer, wherein the polymer is polyethylene glycol. Furthermore, Tan et al. discloses a method of treating a patient having a tumor comprising the step of administering to said patient a therapeutically effective amount of the methioninase-polymer composition.

Page 33 discloses:

Methioninase may be conjugated to a polymer with the purpose of extending its half-life and decreasing its immunogenicity or antigenicity.

Tan et al. does not disclose a reversible process for the conjugation of PEG to methioninase. Additionally, the cited references do not disclose wherein the average 0.7 to 1.3 molecules of a polymer are eliminated per 1 subunit of a protein.

11. It would have been obvious to the ordinary skilled artisan to apply the methods of polymer conjugation to proteins as described by Roberts et al. to the design of a methioninase-polymer composition as described by Tan et al. One of ordinary skill in the art would have recognized that the teachings of Roberts et al. for polymer conjugation would have been readily applicable to any protein that comprises a mercapto group (e.g. cysteine residue), see Figure 8 of Tan et al. Furthermore, the teachings of Tan et al. provide sufficient motivation for the synthesis of PEG conjugated methioninase. Tan et al. teaches that polymer conjugation reduces the antigenicity of the modified protein. One of ordinary skill in the art seeking to restore the antigenicity or activity of a protein comprising modified at the SH groups of cysteine residues would have been motivated to use the reversible process described by Document#2 by treatment with a thiol containing group such as DTT.

12. Regarding the average molecules of polymer eliminated per 1 subunit of a protein, it would have been obvious to the ordinary skill artisan to identify workable ranges by routine experimentation. See MPEP 2144.05.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet Epps-Smith whose telephone number is (571)272-0757. The examiner can normally be reached on M-F, 10AM-6:30PM.

14. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571)-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Janet L. Epps-Smith/  
Primary Examiner, Art Unit 1633